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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,438	02/15/2002	Jeffrey Browning	A080 US CP	3507

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,438	BROWNING ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,11,12,17 and 22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,11,12,17 and 22-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 February 2002 and 10 August 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/10/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 10 August 2005 has been entered in full. Claims 1, 4-7, 11-12, 17, 22-28 are amended. Claims 29-30 are added. Claims 2-3, 8-10, 13-16, 18-21, are cancelled.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1, 4-7, 11-12, 17, and 22-30 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to the drawings at pg 4 of the previous Office Action (07 April 2005) is *withdrawn* in view of the submitted replacement drawings (10 August 2005).

2. The objections to the specification at pg 5 of the previous Office Action (07 April 2005) are *withdrawn in part* in view of the amended title (10 August 2005). Please see section on Specification, below.

3. The objections to claims 1, 4-7, 17-18, and 28 at pg 5 of the previous Office Action (07 April 2005) are *withdrawn* in view of the amended and cancelled claims (10 August 2005).

4. The rejection of claims 23-28 under 35 U.S.C. 112, second paragraph, as set forth at pg 15-16 of the previous Office Action (07 April 2005) is *withdrawn* in view of the amended claims (10 August 2005).

5. The rejection of claims 1, 4-7, 17-18, and 22-28 under 35 U.S.C. § 112, first paragraph (enablement) as set forth at pg 6-13 of the previous Office Action (07 April 2005) is *withdrawn in part* in view of the cancelled and amended claims (10 August 2005). Please see section on 35 U.S.C. § 112, first paragraph (enablement), below.

6. The rejection of claims 1, 4-7, 17-18, and 22-28 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 13-15 of the previous Office Action (07 April 2005) is *withdrawn* in view of the cancelled and amended claims (10 August 2005).

7. The rejection of claims 1, 4-7, 11-12, 17-18, 22-25, and 28 under 35 U.S.C. §102(b) as set forth at pg 16-17 of the previous Office Action (07 April 2005) is *withdrawn* because after reconsideration, Gross et al. (WO/200040716) only contemplates the administration of antibodies.

8. The rejection of claims 1, 4-7, 11-12, 17-18, and 22-27 under 35 U.S.C. § 102(e) as set forth at pg 17-18 of the previous Office Action (07 April 2005) is *withdrawn* because after reconsideration, Shu et al. (US Patent 6,475,987) only contemplates the administration of antibodies. Please see 35 U.S.C. § 102(e), below.

9. The rejections of claims 26 and 28 under 35 U.S.C. § 103(a) as set forth at pg 18-21 of the previous Office Action (07 April 2005) are *withdrawn* in view of paragraphs 5-6 above. Please see section on 35 U.S.C. § 103(a), below.

10. The supplemental information disclosure statement filed on 10 August 2005 has been considered. It is noted that Yu et al. has been crossed off the PTO-1449 because it was previously cited by the Examiner on the PTO-892 form mailed 07 April 2005.

Sequence Compliance

11. The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (10 August 2005) has been considered and is found persuasive. Therefore, the requirements set forth in the Office Action of 07 April 2005 are withdrawn.

Specification

12. The disclosure is objected to because of the following informalities:

12a. At pg 5 of the specification, the Brief Description of the Figures does not refer to Figures 2A-2B. The basis for this objection is set forth at pg 5 of the previous Office Action (07 April 2005).

Appropriate correction is required.

Double Patenting

13. The provisional rejection of claims 1, 4-7, 11, 17-18, 22-23, and 29-30 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 7, and 11 of copending Application No. 10/115,192 as set forth at pg 5-6 of the previous Office Action (07 April 2005) is maintained and held in abeyance until all other issues are resolved. However, Applicant is encouraged to submit a terminal disclaimer at Applicant's earliest convenience. It is noted to Applicant that newly filed claims 29-30 have been added to this rejection for the same reasons of record. Also, in the previous Office Action, claim 23 was inadvertently left out as a typographical error, and the body of the rejection made it clear that the subject matter of the omitted claim was also encompassed by the rejection.

Claim Rejections - 35 USC § 112

14. Claims 4-6, 11-12, 17, 22, and 24-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting B-cell growth or immunoglobulin production, a method for treating a B-cell lymphoproliferate disorder, and a method for treating systemic lupus erythematosus comprising administering to the mammal a therapeutically effective amount of an antibody that specifically binds to a polypeptide consisting

of the sequence of SEQ ID NO: 1, *does not reasonably provide enablement for* methods of treating an autoimmune disease, hypertension, a renal disorder, or inhibiting inflammation comprising the step of administering to the mammal a therapeutically effective amount of an antibody that specifically binds to a polypeptide consisting of the sequence of SEQ ID NO: 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pg 6-13 of the previous Office Action (07 April 2005).

Applicant's arguments (10 August 2005), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that the results and working examples disclosed in the specification provide a direct demonstration of success in inhibiting B-cell growth and treating autoimmune disease by administering a BCMA-BAFF blocking agent. Applicant argues that the skilled artisan would recognize that these results predict success in administering a BCMA-BAFF blocking agent to inhibit immunoglobulin production or inflammation or to treat renal disorders, B-cell lymphoproliferate disorders or hypertension, in view of the fact that B cells and/or dendritic cells are involved in each of these disorders. Applicant indicates that the correlation between the effects of BCMA on B cells and the disorders recited in the claims is reasonable and therefore, the claims are enabled. Applicant also contends that patent laws do not required that all aspects of a pathology be treated, or that a condition be completely cured, for a method of treatment to be enabled. Applicant states that the reasonable expectation of success in treating

the recited conditions is based on the fact that all of the claimed indications involve misregulation of B cells and/or dendritic cells. It is noted that Applicant cites MPEP § 2164.02.

Applicant's arguments have been fully considered but are not found to be persuasive. Although Applicant need not to have actually reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). At pages 12-26, 28-32, and 34, the specification discloses the administration of a "blocking" BAFF-R fusion protein and subsequent reduction of B cell proliferation and treatment of systemic lupus erythematosus. However, the specification also outlines a *prophetic* procedure of "using agents for treating, suppressing, or altering an immune response involving a signaling pathway between BAFF-R and its ligand, and methods of inhibiting inflammation by administering an antibody specific for a BAFF-R or epitope thereof" (pg 4, lines 10-13). Example 12 of the specification (pg 33) states that observations made during phenotypic evaluation of BAFF transgenic mice indicated the potential for hypertension in the mice and "[a]ccordingly, administering a soluble BAFF-R fusion protein or antibody homolog can ameliorate the effects of hypertension" (lines 6-7, 29-30). However, this is not adequate guidance, but is merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The specification of the instant application does not teach any methods or workings examples that indicate an anti-BAFF-R antibody or BAFF-R-Fc fusion protein treats all possible autoimmune diseases, hypertension, renal disorders, or inflammation. As discussed in the previous Office Action of 07 April 2005, the numerous autoimmune diseases and renal disorders encompassed by claims have different pathophysiologies. For example, regarding just autoimmune diseases, rheumatoid arthritis is a

chronic, systemic inflammatory disease that is characterized by synovial inflammation and structural damage of articular cartilage and subchondral bone (pg 325-326; Elgert, K. Immunology, understanding the immune system. New York: Wiley-Liss, Inc., 1996). Graves' disease is a disorder of the thyroid gland that is caused by autoantibodies that stimulate thyroid cellular activity by displacing thyroid-stimulating hormone binding (Elgert, K., pg 324, col 2). Asthma is characterized by a constriction of the bronchioles of the lung wherein the tissue surrounding the capillaries of the lung contains mast cells, which, when stimulated by allergen, release histamine, causing contraction of the smooth muscles (Elgert, K., pg 305, col 2). Undue experimentation would be required of the skilled artisan to administer an anti-BAFF-R antibody to individuals with all possible autoimmune disorders and diseases and treat the disorder or disease. One skilled in the art would also not be able to predict from the instant specification that an anti-BAFF-R antibody would be able to treat all possible autoimmune disorders (such as rheumatoid arthritis and Graves' disease) and renal disorders, which have different pathophysiologies. Increased B cell activity is not the only characteristic of autoimmune diseases and renal disorders and BAFF-R is not the only stimulant of B cells, particularly B cells directed to produce antibodies to self antigens as in autoimmune diseases.

Additionally, although Applicant states that all of the claimed indications involve misregulation of B cells and/or dendritic cells, the Examiner is unable to determine the nexus between B cells, BAFF-R, and inflammation and hypertension. It is noted that the specification only discloses that BAFF transgenic mice have a tendency towards hypertension (or no statistical significance), as compared to negative control mice. There is no nexus that merely administering an anti-BAFF-R antibody the binds to protein of SEQ ID NO: 1 to an individual in need thereof

can reasonably be extrapolated to successfully treat any subject experiencing inflammation or hypertension, as claimed, without undue experimentation to determine such. The examples in the specification of the instant application only indicate that administration of the "blocking" BAFF-R-Fc fusion protein inhibits B cell proliferation and treats systemic lupus erythematosus (see pg 12-26, 28-32, and 34). It must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37; *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979).

Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat all possible autoimmune diseases, renal disorders, hypertension, or inflammation by administration of an anti-BAFF-R antibody.

(ii) Applicant also argues that the skilled artisan would know how to make antibodies that specifically bind the polypeptides recited in the claims. Applicant states that the specification provides ample guidance. Applicant points out that the disclosure teaches the skilled artisan how to use these antibodies, particularly in Examples 8-9, 11, 13, and 14 (pages 23-34). Applicant submits that these results provide a direct demonstration of success in inhibiting B-cell growth and treating autoimmune disease by administering a BCMA-BAFF blocking agent. Applicant asserts that the skilled artisan would also understand that antibodies against BCMA are alternatives to soluble BCMA fusions. Applicant argues that antibodies are not only alternatives to BCMA-Ig fusions, but antibodies can actually be more effective blocking agents. Applicant cites *In re Borkowski*, 422 F.2d 904,908, 164 USPQ 642, 645 (CCPA) to emphasize that working examples are not required. Applicant asserts, though, that the disclosure does provide working examples.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, there is insufficient guidance and direction as to make and use anti-BAFF-R antibodies wherein the antibodies bind a BAFF-R polypeptide that is at least 95% identical to amino acid residues 1 to 184 of SEQ ID NO: 1. The genus encompasses antibodies that can bind BAFF-R polypeptides wherein such BAFF-R polypeptides have numerous differences in amino acid sequences, including numerous differences in linear and conformational epitopes. However, the present specification fails to provide sufficient disclosure of such BAFF-R polypeptides that maintain the structural and functional properties of the BAFF-R polypeptide set forth in SEQ ID NO: 1. The specification does not provide sufficient guidance as to which of the amino acids may be changed while BAFF-R structural or functional activity and specificity is retained. For

example, Lederman et al. (Mol Immunol 28: 1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Li et al. (Proc Natl Acad Sci USA 77: 3211-3214, 1980) also disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document). Because of this lack of guidance, the extended experimentation that would be required to determine which modifications would be acceptable to retain occluding structural and functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (see Ngo et al., for example), it would require an undue amount of experimentation for one of skill in the art to arrive at the other BAFF-R polypeptide encompassed by the claimed invention. The art recognizes that function cannot be predicted from structure alone (Bork, 2000; Skolnick et al., 2000; Doerks et al.; Smith et al., 1997; Brenner, 1999; Bork et al., 1996). Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make use the claimed BAFF-R specific antibodies in a manner reasonably correlated with the scope of the claims broadly including a broad number of structural changes encompassed by 95% sequence identity. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the BAFF-R encoding nucleic acids and amino acids and still maintain biological activity or structural specificity of BAFF-R is unpredictable and the experimentation left to those skilled in the art is extensive and undue.

Furthermore, although Applicant needs to not actually have reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be

considered, especially in a case involving an unpredictable art (MPEP § 2164.02). It is noted that the fact pattern of the case cited by the Applicant (*In re Borkowski*) and the fact pattern of the instant rejection are significantly different, and the court decision is not binding with regard to the instant rejection. For example, in *Borkowski*, the claims are drawn to a process for producing oxygenated hydrocarbons. The Court of Customs and Patent Appeals indicated that the specification need not contain a working example if one skilled in the art could practice it without undue experimentation and considering the nature of the claimed invention (process for producing hydrocarbons), the few hours of experimentation required were not an undue amount of time. However, the case cited by Applicant does not have claims directed to an antibody or methods of treatment using an antibody.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to (1) treat all possible autoimmune diseases, renal disorders, hypertension, and inflammation, and (2) generate all possible BAFF-R derivatives that are 95% identical to SEQ ID NO: 1 and anti-BAFF-R antibodies, and (3) generate all possible antigenic determinants of the BAFF-R polypeptide and generate antibodies thereto; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the unpredictability of treating all possible autoimmune diseases, renal disorders, hypertension, or inflammation and the unpredictability of the effects of protein alterations on antibody binding, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
25 October 2005

ELIZABETH KEMMERER
PRIMARY EXAMINER